WITHDRAWAL OF *STAPHYLOCOCCUS AUREUS* FROM INTENSIVE CARE UNITS IN TURKEY

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* **ICU Infection Study Group**; Overall, 28 universities, 8 training and research hospitals; total of 36 Turkish tertiary care centers joined this study.

INTRODUCTION

Staphylococcus aureus and methicillin-resistant *S. aureus* (MRSA) in particular, have been causing major problems in the hospitals throughout the world. After the recovery in 1961, MRSA remained uncommon for a while. However, by the late 1960s a multi-resistant MRSA clone was continuously reported from a number of countries. Although this strain was extensively disseminated, its prevalence declined in late 1970s. The reasons of these trends were not completely understood. On the other hand, MRSA reappeared in the early 1980s and significant increments were noted inside the hospitals during the entire 1990s. According to the National Nosocomial Infections Surveillance System data related to MRSA in the US hospitals, the prevalence increased from 2% in 1975 to 35% in 1991. This trend kept on and the prevalence of *S. aureus* infections inclined from 0.74% of all hospitalized patients in 1998 to 1% in 2003 in USA. In fact, similar profiles were seen in the other parts of the world and Europe. Nevertheless, in 21st century, there were initial evidences that the pattern of *S. aureus* infections will change. For example, a multicenter study from France reported decreasing MRSA infection incidence and methicillin resistance rates. Accordingly, a reduction in MRSA infection and transmission was noted in United Kingdom. Although preliminary data exist on this issue, a strict documentation is lacking on the unstable epidemiology of ICU infections; in particularly *S. aureus.* Since there may be significant variations in the epidemiology of *S. aureus* infections even between the neighboring communities, obtaining the big picture is crucial in decision making. Therefore, the aim of this multicenter study was to trace the epidemiological changes and the probable shifts in the intensive care units (ICUs) of tertiary hospitals in Turkey.

METHODS

Study design and patient population
This retrospective study was performed in the first three months (January 1st – March 31st) of 2008 and 2011 in different ICUs of Turkey. No informed consent was required, but the study was approved by local ethics committee. All hospitalized patients in the ICUs for above mentioned dates were eligible for this study.
Data collection and definitions
In Turkey data related to HAIs are regularly collected according to CDC criteria by national HAI surveillance network, which serves as a department in Turkish Ministry of Health. This network was organized to collect data from state, training and research, university, and private hospitals in 2006. Since then, increasing number of hospitals started to enter their data to this network. All of the study centers are selected from tertiary hospitals which provide data regularly to the national network in both 2008 and 2011. Since some of the centers joined the national database after 2008, the hospitals which did not perform this surveillance in both periods were excluded from the study. The participation to this study was on the voluntary basis. Two centers could not join the study, one due to an earthquake preceding the study and the other one due to its heavy workload. As a result, 88 ICUs from 36 tertiary hospitals have participated in the study.
Hospital-acquired infections (HAI) surveillance has been performing actively based on both laboratory and patient records in the participant ICUs. Study data was obtained from the local infection control committee records of each participant center through two separate questionnaires. One included general information about the ICU (number of patients, nurses, availability of a fully responsible specialist, isolation rooms for each ICU, length of hospital stay (LOS) for each patient, number of central line- days, number of ventilator-days, number of urinary catheter-days, number of HAI causing pathogens and HAI sites etc. for the first three months of 2008 and of 2011). The other questionnaire included the demographic and clinical characteristics of all patients with *S. aureus* infection in the ICUs at the relevant periods. Only one isolate of the same species per patient was included in the study. The diagnosis of HAI was made according to the criteria of the Centers for Diseases Control and Prevention (CDC).

RESULTS

Overall, 28 universities, 8 training and research hospitals; total of 36 Turkish tertiary care centers joined this study. Overall 88 ICUs were enrolled in our study. The current sum of bed capacities of these hospitals was 30,745. The sum of the bed capacities of the participant ICUs in the first quarters of 2008 and 2011 were 1,007 and 1,126 respectively. The distribution of the 88 participant ICUs: Thirty-nine (44.3%) mixed, 9 (10.2%) general surgery, 9 (10.2%) neurosurgery, 9 (10.2%) internal medicine, 8 (9.1%) cardiac surgery, 7 (8%) neurological, 6 (6.8%) pulmonology, and one (1.1%) burns ICUs.
The ICU patient and invasive device characteristics between 2008 and 2011 are compared. However it does not seem statistically significant, the availability of a fully responsible specialist in the ICUs was increased between the two periods (n=52 *vs.* n=59; p=0.031). On the other hand, the availability of isolation rooms in the ICUs was significantly increased between the two periods (n=39 *vs.* n=57; **p<0.0001**).
The HAI density in Period 1 (P1) was 32.3 and 30 in Period 2 (P2) (**p=**0.017). Central line (**p<0.0001**), ventilator (**p<0.0001**) and urinary catheter utilization ratios (**p<0.0001**) increased significantly in P2. and the rates of central line-associated blood stream infection, ventilator-associated pneumonia and catheter-associated urinary tract infection were not significantly different between P1 and P2 (p>0.01; Table 1).
The proportion of *S. aureus* in responsible bacteria was significantly lower in 2011 than that of 2008 was (7.3% vs. 15%; **p<0.0001**). Accordingly, the MRSA proportion was also significantly lower in 2011 than that of 2008 was (5.5% *vs.* 12.7%; **p<0.0001**). In contrast, the proportion of *Acinetobacter* spp. was significantly higher in 2011 than that of 2008 was (28.6% *vs.* 21.9%; **p<0.0001**). No statistical significant differences were detected in terms of *Pseudomonas aeruginosa*, enteric Gram-negative bacilli, Coagulase-negative staphylococci (CoNS), enterococci, *S. maltophilia* and *Candida* spp. related HAIs between the two periods (p>0.01; Table 2).
The incidence density of *S. aureus* and MRSA to HAIs in the participant ICUs between the years of 2008 and 2011 are shown in Table 3. The density of HAIs due to *S. aureus* was significantly lower (2.25) in 2011 than that of 2008 was (4.23) (**p<0.0001**) and the same declining trend in MRSA responsible HAIs density was also found between the two periods (1.68 *vs.* 3.59; **p<0.0001**). Catheter-related BSI density due to *S. aureus* was 2.09 in P1 and 0.85 in P2 (**p<0.00001**) and the same HAI caused by MRSA for P1 and P2 were 1.81 and 0.67, respectively (**p<0.00001**). Also, the density of VAP due to *S. aureus* was 4.48 in P1 and, it was 2.12 in P2 (**p<0.00001**) and the density of MRSA related VAP was 4 in P1 and 1.65 in P2 (**p<0.00001**).

Table 1. Invasive device usage and the incidence densities of hospital-acquired infections (HAIs) in participant intensive care units (ICUs)

Incidence Density*/ Device Utilization Ratio	2008	2011	Chi-square	Difference (95% CI)	p value
Hospital-acquired infection	2164/67068 (32.3) (95%CI: 30.9-33.6)	2276/75800 (30.0) (95%CI: 28.8-31.3)	5.74	2.2 (0.4-4)	0.017
Central line-associated blood stream infection	245/31973 (7.7) (95%CI: 6.7-8.7)	279/38692 (7.2) (95%CI: 6.4-8.1)	0.48	0.05 (0.08-0.17)	0.49
Central line-utilization ratio	31973/67068 (47.7 %) (95%CI: 47.2%-48.2%)	38692/75800 (51.0%) (95%CI: 50.5%-51.6%)	159.7	3.34 (2.82-3.86)	<**0.0001**
Ventilator associated pneumonia	715/29442 (24.2) (95%CI: 22.5-26.1)	883/38602 (22.8) (95%CI: 21.3-24.4)	1.41	0.14 (0-0.37)	0.23
Ventilator utilization ratio	29442/67068 (43.9%) (95%CI: 43.4%-44.4%)	38602/75800 (50.9%) (95%CI: 50.4%-51.4%)	698.8	7.0 (6.5-7.5)	<**0.0001**
Catheter-associated urinary tract infection	394/52968 (7.43) (95%CI: 6.7-8.2)	477/64559 (7.38) (95%CI: 6.7-8.1)	0.98	0.05 (0-1.0	0.92
Urinary catheter-utilization ratio	52968/67068 (78.9%) (95%CI: 78.5%-79.6%)	64559/75800 (85.2%) (95%CI: 84.5%-85.8%)	966.7	6.3 (5.9-6.7)	<**0.0001**

Table 2. Pathogen microorganisms responsible for hospital-acquired infections (HAIs) in participant intensive care units (ICUs)

Microorganism	2008 (N=1892)No (%)	2011 (N=2339)No (%)	Chi-square	Difference (95% CI)	p value
S. aureus*	284 (15)	172 (7.3)	63.85	7.7 (5.76-9.67)	<**0.0001**
(MRSA)	241 (12.7)	128 (5.5)	67.25	7.2 (5.42-9.02)	<**0.0001**
CNS	110 (5.8)	139 (5.9)	0.01	0.10 (0-1.54)	0.943
Enterococci	158 (8.3)	173 (7.4)	1.06	0.90 (0-2.58)	0.304
Other Gram (+) cocci	21 (1.2)	18 (1)	0.23	0.20 (0-0.90)	0.635
***Acinetobacter* spp.**	414 (21.9)	671 (28.6)	24.31	6.7 (4-9.33)	<**0.0001**
P. aeruginosa	262 (13.8)	353 (15.1)	1.32	1.30 (0-3.45)	0.25
Escherichia coli	192 (10.1)	227 (9.7)	0.15	0.40 (0-2.26)	0.703
***Klebsiella* spp.**	163 (8.6)	194 (8.3)	0.09	0.30 (0-2.04)	0.769
***Enterobacter* spp.**	45 (2.4)	55 (2.3)	0.01	0.10 (0-1.08)	0.911
S. maltophilia	21 (1.1)	26 (1.1)	0.02	0.40 (0-0.66)	0.882
Other Gram (-) bacilli	60 (3.3)	102 (4.4)	3.09	1.1 (0-2.29)	0.079
***Candida* spp.**	162 (8.5)	209 (8.9)	0.16	0.40 (0-2.13)	0.686

Table 3. The incidence densities of *Staphylococcus aureus* and MRSA according to hospital-acquired infections in the participant ICUs (2008-2011)

Microorganism	2008	2011	Chi-square	Difference (95% CI)	p value
Staphylococcus aureus					
Catheter-related BSI	67/31973 (2.09) (95%CI: 1.6-2.7)	33/38692 (0.85) (95%CI: 0.59-1.19)	19.10	1.24 (0.69-1.8)	**0.00001**
Ventilator associated pneumonia	132/29442 (4.48) (95%CI: 3.75-5.32	82/38602 (2.12) (95%CI: 1.69-2.64)	29.56	2.36 (1.51-3.21)	<**0.00001**
Catheter associated UTI	8/52968 (0.15) (95%CI: 0.06-0.29)	7/64559 (0.11) (95%CI:0.02-0.18)	0.41	0.043 (0-0.172)	0.52
Overall	284/67068 (4.23) (95%CI: 3.76-4.76)	172/75800 (2.25) (95%CI: 1.93-2.62)	43.06	1.96 (1.38-2.55)	<**0.00001**
Methicillin-resistant *S. Aureus (MRSA)*					
Catheter-related BSI	58/31973 (1.81) (95%CI: 1.37-2.34)	26/38692 (0.67) (95%CI: 0.44-0.98)	19.21	1.14 (0.63-0.165)	**0.00001**
Ventilator associated pneumonia	118/29442 (4.00) (95%CI: 3.32-4.80)	64/38602 (1.65) (95%CI: 1.28-2.12)	34.48	2.35 (1.57-3.13)	<**0.00001**
Catheter associated UTI	8/52968 (0.15) (95%CI: 0.06-0.29)	5/64559 (0.08) (95%CI: 0.02-0.18)	1.42	0.07 (0-0.19)	0.23
Overall	241/67068 (3.59) (95%CI: 3.15-4.07)	128/75800 (1.68) (95%CI: 1.41-2.00)	49.98	1.90 (1.38-2.43)	<**0.00001**

CONCLUSİONS

The incidence density of HAIs were similar to other developing countries. According to our multicenter ICU study, the infections due to both *S. aureus* and MRSA decreased significantly in 2011 compared to the 2008 period, while the decrease in overall HAIs was not significant. These data were in accordance with significant declines in *S. aureus* and MRSA invasive device associated infections, which reflect the most critical changes in hospital epidemiology.
According to the results of the study, invasive device utilization did not decrease in 2011 compared to 2008 period and in contrast, there were significant increase in central line, urinary catheter and ventilator utilization in the latter period along with increases in sum of hospital stays and the number of patients hospitalized in the ICUs. However, infections related to invasive devices did not increase significantly. All these data can be interpreted as the efficacy of improving infection control practices. Thus, VAP and CLABSIs due to *S. aureus* and MRSA were seen significantly less frequently in Turkish ICUs in the second period. On the other hand, the situation was not the same for CAUTIs probably due to very low number of staphylococcal CAUTIs in our study.
The new millennium has witnessed the emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli. *Acinetobacter baumannii*, *P. aeruginosa* and *Klebsiella pneumoniae* are particularly the foci of concerns in this context either in the hospital wards or in the ICUs. According to our data, the isolation of *Acinetobacter* spp. has increased in 2011 period compared to 2008. Interestingly, this trend was not shared by any other group of microorganisms like *P. aeruginosa*, enteric Gram-negative bacilli, CoNS, enterococci or *Candida*. The most frequent infections related to *Acinetobacter* spp. are VAP, bacteremia, surgical-site infections and urinary tract infections in the ICUs. Hence, this increase will and still has serious impacts on the ICU patients. Thus, the question is “why *Acinetobacter* spp. is on the rise while *S. aureus* withdraws from the scene”. The answer may lie in the rapid ability in transformation of *Acinetobacter* spp. surviving desiccation, persistence in the environment for a very long time and resistance to a wide range of antimicrobials. Although recommendations to prevent MRSA have well been validated, there is a paucity of data for multifaceted interventions to prevent multidrug resistant *A. Baumannii*. Since previous investigations have reported that collaborative infection control efforts were associated with declines in HAIs, the benefits of such interventions were uncertain for the control of infections related to multidrug resistant pathogens. That may be an explanation for our insufficiency in controlling the accelerated *Acinetobacter* infection trend despite rigorous infection control in the ICUs. Today, *Acinetobacter* infections in ICUs in Turkey imposed a real dilemma to the clinician, since carbapenem resistance is around 70% in the hospitals, which mostly reflects the ICU isolates, according to the Turkish National Nosocomial Infections Surveillance Network (UHESA) data. This datum can also be interpreted as the difficulty in eradicating the infecting *Acinetobacter* strains compared to *S. aureus*, which has many efficient therapeutic modalities.
In conclusion, the strengths of our study are its multicenter form, the collection of a high volume of data, and the presentation of results only with high statistical significance although its weakness is the retrospective and observational design. To the best of our knowledge, our data seem to document another microbial shift in medical practice as in 1970s and the reasons of the current trend are not entirely known like the previous experiences. Hence, our study suggests the reconsidering of anti-Gram positive agent use on the empirical basis since the impact of *S. aureus* declines significantly. It appears that in accordance with the decline of *S. aureus* infections from the ICUs *Acinetobacter* spp. take over the place.